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A number of cytokines including the family of interleukins and the macrophage inflammatory proteins act in the brain to produce fever. The purpose of this study was to determine whether the recently discovered hematopoietic progenitor cell stimulator, interleukin-11 (IL-11), alters the body temperature (Tb) of the rat when the cytokine is delivered directly to the thermosensitive and pyrogen reactive region of the hypothalamus. A guide cannula for micro-injection into the anterior hypothalamic pre-optic area (AH/POA) was implanted stereotaxically in each of 19 male Sprague-Dawley rats. A Mini-mitter transmitter for continuous monitoring of Tb of the animal was implanted i.p. Following postoperative recovery, recombinant human IL-11 was micro-injected in a volume of 1.0 microliter into the AH/POA in a dose of 2.7, 13.5, 27 or 250 ng. rhuIL-11 evoked a dose dependent fever with a mean rise in Tb of 0.91 +/- 0.06 degrees C, 1.68 +/- 0.11 degrees C and 0.99 +/- 0.08 degrees C following 13.5 ng, 27 ng and 250 ng, respectively. No significant change in Tb of the rats was produced by 2.7 ng IL-11 or the CSF control vehicle. A significant decline in the intake of food occurred also after the micro-injection of the 27 ng of IL-11. Prior treatment of the rat with 5.0 mg/kg of a prostaglandin synthesis inhibitor, indomethacin, administered intraperitoneally attenuated significantly the febrile response induced by the 250 ng dose of IL-11. These results demonstrate that IL-11 possesses potent thermogenic properties when acting within the ventral forebrain.(ABSTRACT TRUNCATED AT 250 WORDS)

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Fever Produced by Interleukin-11 (IL-11) Injected into the Anterior Hypothalamic Pre-optic Area of the Rat is Antagonized by Indomethacin

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Summary—A number of cytokines including the family of interleukins and the macrophage inflammatory proteins act in the brain to produce fever. The purpose of this study was to determine whether the recently discovered hematopoietic progenitor cell stimulator, interleukin-11 (IL-11), alters the body temperature (T_b) of the rat when the cytokine is delivered directly to the thermosensitive and pyrogen reactive region of the hypothalamus. A guide cannula for micro-injection into the anterior hypothalamic pre-optic area (AH/POA) was implanted stereotactically in each of 19 male Sprague-Dawley rats. A Mini-mitter transmitter for continuous monitoring of T_b of the animal was implanted i.p. Following postoperative recovery, recombinant human IL-11 was micro-injected in a volume of 1.0 μ l into the AH/POA in a dose of 2.7, 13.5, 27 or 250 ng. rhIL-11 evoked a dose dependent fever with a mean rise in T_b of $0.91 \pm 0.06^\circ\text{C}$, $1.68 \pm 0.11^\circ\text{C}$ and $0.99 \pm 0.08^\circ\text{C}$ following 13.5 ng, 27 ng and 250 ng, respectively. No significant change in T_b of the rats was produced by 2.7 ng IL-11 or the CSF control vehicle. A significant decline in the intake of food occurred also after the micro-injection of the 27 ng of IL-11. Prior treatment of the rat with 5.0 mg/kg of a prostaglandin synthesis inhibitor, indomethacin, administered intraperitoneally attenuated significantly the febrile response induced by the 250 ng dose of IL-11. These results demonstrate that IL-11 possesses potent thermogenic properties when acting within the ventral forebrain. IL-11 induces a fever by its action directly on neurons of the AH/POA and in an order of potency corresponding to that of other interleukins. Further, the mechanism of action underlying the febrile response to IL-11 could involve the cyclo-oxygenase pathway and the localized diencephalic synthesis of a prostaglandin rather than the functionally independent macrophage inflammatory protein-1 pathway.

Keywords—Interleukin-11, fever, cytokines, body temperature, thermoregulation, anterior hypothalamus, prostaglandins, indomethacin, hyperthermia, macrophage inflammatory protein-1 β (MIP-1 β).

Interleukin 11 (IL-11) is a novel cytokine identified originally in the PU-34 bone marrow-derived stromal cell line of the primate (Paul *et al.*, 1990). An initial biological characterization of this 199-amino acid polypeptide showed that it stimulated the proliferation of an interleukin 6 (IL-6)—dependent murine plasmacytoma cell line (Paul *et al.*, 1990). Although one of the principal targets of IL-11 seems to be the hematopoietic progenitor cells (Hangoc *et al.*, 1993), this cytokine has been reported to have diverse effects on distinct biological systems. For example, IL-11 *in vitro* promotes the maturation of murine and human megakaryocytes (Burstein *et al.*, 1992; Kobayashi *et al.*, 1993) and exerts a stimulatory effect on several myeloid/erythroid systems (Quesniaux *et al.*, 1993). *In vivo*, IL-11 increases both the

number of neutrophils and platelets in peripheral blood and enhances megakaryocytopoiesis in the mouse (Du *et al.*, 1993; Neben *et al.*, 1993; Hangoc *et al.*, 1993). Apart from this activity, IL-11 stimulates the synthesis of acute phase proteins by hepatocytes (Baumann and Schendel, 1991) and inhibits adipogenesis as well as lipoprotein lipase activity (Yin *et al.*, 1992). In certain cases, the action of IL-11 has been found to be synergistic with other cytokines such as IL-1 and IL-3 (Burstein *et al.*, 1992; Hu *et al.*, 1993), which reflects the existence of specific receptors for the cytokine on the cell surface (Baumann and Schendel, 1991).

Over the last two decades, many studies have demonstrated that different cytokines act centrally to produce an increase in body temperature (T_b) when they are applied directly to the area of the diencephalon which contains thermosensitive neurons (Myers *et al.*, 1993; Miñano *et al.*, 1990). For example, IL-1 and IL-6

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micro-injected into the anterior hypothalamic, preoptic area (AH/POA) evoke a fever in the rat and other species (Blatteis *et al.*, 1990; Myers *et al.*, 1994; Morimoto *et al.*, 1989; Opp *et al.*, 1989). The purpose of the present experiments was to determine, therefore, whether IL-11 also possesses a biological action on the central nervous system. In this study, IL-11 was injected in different doses at sites within the thermosensitive and pyrogen reactive region of the AH/POA (Myers, 1974; 1980; Miñano *et al.*, 1991) to examine its action on the T_b of the rat as well as on its ingestion of food and water. In addition, an inhibitor of prostaglandin (PG) synthesis, indomethacin, was given prior to IL-11 in order to determine whether a PG of the E series could play a possible role in the physiological response to IL-11.

METHODS

Male Sprague-Dawley rats ($n = 19$) weighing 323 ± 14 g were housed individually in a laboratory room kept at a temperature of $22 \pm 1.5^\circ\text{C}$ and on a 12 h illumination cycle with lights on from 0730–1930 hr. Water and Purina Formulab No. 5008 rodent food were provided *ad lib* to each animal, and their intake as well as body weight were recorded daily.

Surgical procedures

Each rat was anesthetized with 45–50 mg/kg of sodium pentobarbital injected i.p. and placed in a Kopf stereotaxic instrument. Following aseptic surgical procedures (Myers *et al.*, 1993), a 20 ga thin-walled stainless steel guide tube enclosed in a pedestal was implanted stereotaxically so that the tip of the guide was positioned 6.0 mm ventral to the dura mater in the region just dorsal to the AH/POA with the coordinates: AP 8.0 to 9.0; LAT 0.7 to 0.8; HOR -5.0 to -6.0 (Paxinos and Watson, 1986). A 23 ga stylet of identical length and bevel was inserted into the guide tube to prevent its occlusion. In a second procedure, a radio transmitter (Mini-Mitter, Sunriver, OR), which transmitted temperature signals to a computer-linked receiver, was placed in the intraperitoneal cavity so that the core T_b of the rat was recorded continuously (Barwick and Myers, 1993). Postoperatively during a period of 6–7 days, each rat was acclimatized to the experimental conditions so that no restraint was required.

Micro-injection procedures

A micro-injection of an artificial CSF vehicle (Myers, 1977) or cytokine into the AH/POA was made over an interval of 1.0 min through a 28 ga stainless steel needle connected by a PE 20 tubing to a Hamilton gas-tight microliter syringe mounted on an infusion pump. Pyrogen-free CSF was passed through a 0.22 μm Acrodisc non protein binding filter (Gelman Sciences, Ann Arbor, MI) and flushed repeatedly through the injection system prior to each experiment.

Following postoperative recovery, sites were identified in the AH/POA of each rat which were reactive to a fever-inducing cytokine. For these experiments, an efficacious test dose of 28 pg of recombinant murine macrophage inflammatory protein-1 β (rmuMIP-1 β) (Genetics Institute, Cambridge, MA) in the pyrogen-free artificial CSF vehicle was micro-injected in a volume of 1.0 μl at incremental depths below the guide tube. When the micro-injection of MIP-1 β raised the T_b of the rat by $\geq 0.5^\circ\text{C}$ within 0.5 hr and for an interval of at least 4.0 hr, the site was denoted as reactive to cytokine. Thereafter, a micro-injection was given only at a site identified as reactive to the febrile effect of MIP-1 β .

In the dose response phase of the experiments, recombinant human IL-11 (Batch No. 2284:81, Genetics Institute, Cambridge, MA), with a specific activity of 2.52×10^6 U/mg was micro-injected into the AH/POA of 14 rats in a dose of 2.7, 13.5 or 27 ng/ μl . The CSF control vehicle was given in an identical manner at homologous sites in the AH/POA. The order of the micro-injection of each dose of IL-11 and the CSF vehicle was randomized, and ordinarily no more than four injections were given at a reactive site. Successive experiments which were separated by an interval of 24 hr were carried out between 0830 and 1000 hr.

In a second group of five rats, indomethacin (Sigma, St Louis, MO), dissolved in a saline vehicle containing 20% ethanol and 4% NaHCO_3 , was injected i.p. in a standard dose of 5.0 mg/kg (Hashimoto, 1991; Miñano *et al.*, 1990; 1991) 15–20 min before the micro-injection into the AH/POA of 250 ng IL-11 (Batch No. NW2570120, Genetics Institute, Cambridge, MA), which had a lower specific activity of 1.5×10^6 U/mg than that of Batch No. 2284:81.

Histological and statistical analyses

At the conclusion of the experiments, each rat was given an overdose of sodium pentobarbital and perfused transcardially with buffered neutral formalin. Then the brain was removed, 100 μm sections were cut in the coronal plane on a cryostat, mounted and stained with cresyl violet following standard procedures. Anatomical maps were constructed which depicted each site of micro-injection following its histological identification under light microscopy.

Means and standard errors of the T_b responses at each time interval and maximal rise in T_b were calculated for the different groups. The data were analyzed using the Instat software program (GraphPAD, San Diego, CA) by analyses of variance followed by Student Newman-Keuls tests. A P value of <0.05 was considered to be statistically significant.

RESULTS

A neuroanatomical mapping of the sites of micro-injection of the four doses of rhuIL-11 is presented in Fig. 1; the artificial CSF control vehicle also was

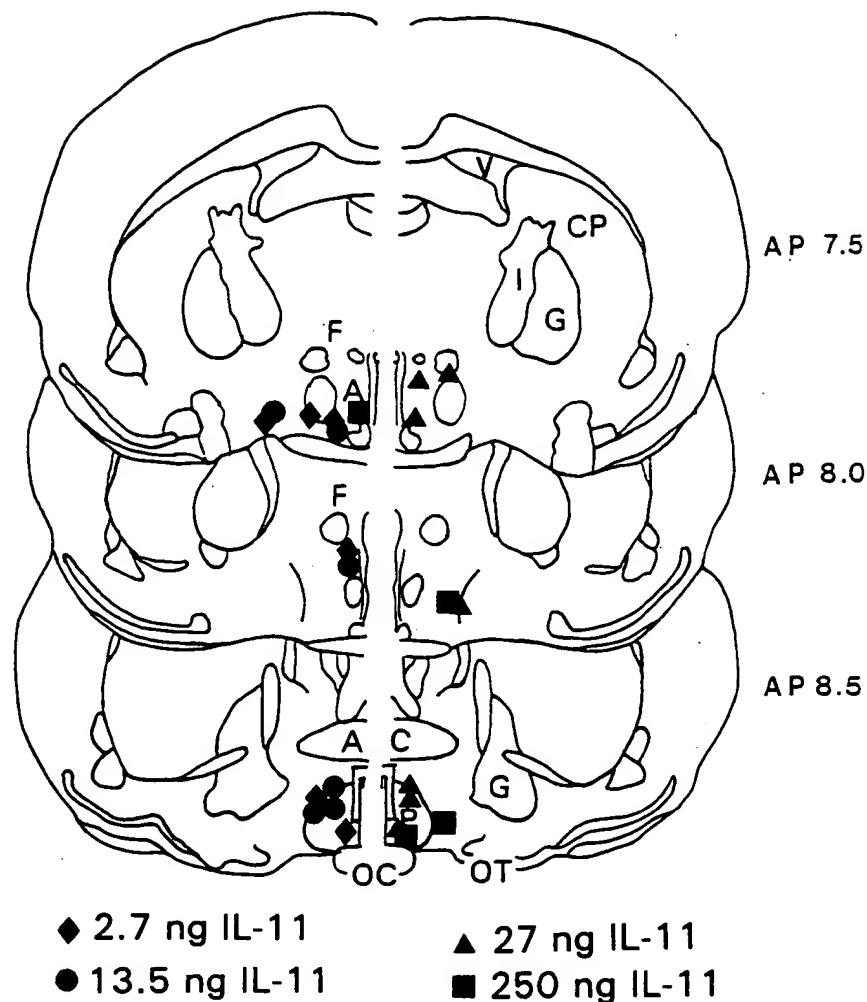


Fig. 1. Composite anatomical mapping of individual sites of micro-injection, localized within coronal planes AP 7.5, 8.0 and 8.5, of: 2.7 ng IL-11 (diamond, $N = 6$); 13.5 ng IL-11 (circle, $N = 8$); 27 ng IL-11 (triangle, $N = 8$); and 250 ng IL-11 (square, $N = 5$). N = number of experiments. Anatomical abbreviations are: A, anterior hypothalamus; AC, anterior commissure; CP, caudate putamen; F, fornix; G, globus pallidus; I, internal capsule; OC, optic chiasm; OT, olfactory tubercle; P, medial preoptic area; V, lateral cerebral ventricle.

micro-injected at most of these loci. The region in which the micro-injections of IL-11 induced significant increases in the T_b of the rat was localized within coronal planes AP 7.5, AP 8.0 and AP 8.5 in an area ventral to the anterior commissure and dorsal to the optic chiasm. These loci encompass the anterior hypothalamus and the medial pre-optic area (Fig. 1) which comprise the classical thermosensitive and pyrogen reactive regions of the diencephalon.

Temperature responses

As shown in Fig. 2, the micro-injection of IL-11 into the AH/POA induced a dose-dependent fever in the rat. The highest dose of 27 ng IL-11 increased the mean T_b to $1.68 \pm 0.11^\circ\text{C}$ with a peak of $2.06 \pm 0.20^\circ\text{C}$ at the 3.0 hr interval after the micro-injection. This rise was statistically different from both the T_b response to the control CSF ($F_{[1,175]} = 260.9$, $P < 0.01$) and the 2.7 ng dose of IL-11 ($F_{[1,111]} = 138.4$, $P < 0.01$). The dose of

13.5 ng IL-11 also produced a significant rise in T_b of 0.91 ± 0.06 , which peaked at $1.14 \pm 0.35^\circ\text{C}$ at the 5.0 hr period following the injection (Fig. 2). The T_b rise in response to this intermediary dose of the cytokine was significantly different from that of the control CSF ($F_{[1,175]} = 138.5$, $P < 0.01$) and the 2.7 ng dose of IL-11 ($F_{[1,111]} = 98.2$, $P < 0.01$). The increases in T_b elicited by the 13.5 ng and 27 ng doses of IL-11 were also significantly different from one another ($F_{[1,127]} = 37.8$, $P < 0.01$). However, the initial increases in T_b , which typically occurred within the first 0.5 hr following a micro-injection, were not statistically significant and were due likely to the procedure itself. As portrayed in Fig. 3, the mean maximum rise in T_b of the groups of individual rats was $1.56 \pm 0.3^\circ\text{C}$ and $2.4 \pm 0.17^\circ\text{C}$ after the 13.5 ng and 27 ng doses of IL-11, respectively. However, the T_b of the rats did not differ in response to the lowest dose of 2.7 ng IL-11 and the CSF vehicle.

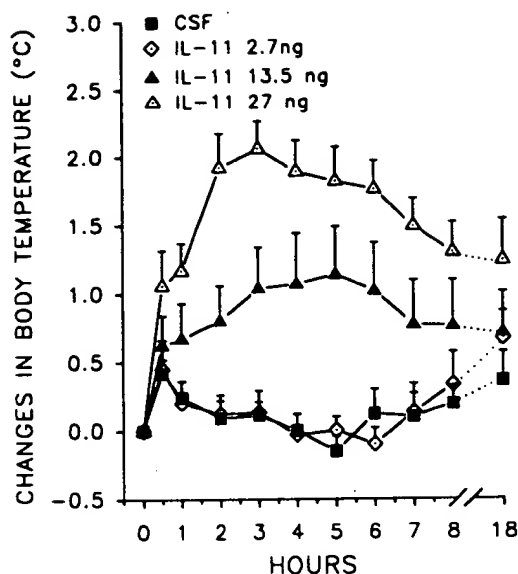


Fig. 2. Mean \pm SE change from baseline T_b ($^{\circ}\text{C}$) at time zero of rats after micro-injection into AH/POA of CSF control ($N = 15$), 2.7 ng IL-11 ($N = 6$); 13.5 ng IL-11 ($N = 8$); and 27 ng IL-11 ($N = 8$). N = number of experiments. The mean baseline T_b at zero time was 37.0°C .

Feeding responses

As shown in Table 1, the 27 ng dose of IL-11 micro-injected into the AH/POA of the rats reduced significantly the intake of food over the 24 hr period after its micro-injection in comparison to that following the CSF control injection ($F_{[1,21]} = 14.49$, $P < 0.01$). However, no statistically significant differences arose in the intakes of food and water or in the body

Table 1. Mean \pm SE change in body weight, intakes of food and water 24 hr after micro-injections of CSF or three doses of IL-11 into the AH/POA of the rat

	Weight (g)	Food (g)	Water (ml)
Control	2.41 ± 2.30	1.71 ± 1.05	0.21 ± 2.67
IL-11 27 ng	-2.37 ± 5.94	$-6.25 \pm 2.09^*$	-5.25 ± 2.83
IL-11 13.5 ng	1.50 ± 2.47	-0.87 ± 1.85	0.00 ± 2.38
IL-11 2.7 ng	-0.83 ± 2.27	1.33 ± 0.92	0.83 ± 2.57

* $P < 0.05$.

weight after the CSF and other two doses of IL-11 (Table 1).

Indomethacin pretreatment

The micro-injection into the AH/POA of the rat of 250 ng of the IL-11 Batch No. NW2570120, which had a much lower specific activity of 1.5×10^6 U/mg as compared to that used in the dose response study, elicited a fever which reached a mean level of $1.46 \pm 0.15^{\circ}\text{C}$ at the 6.0 hr interval. As shown in Fig. 4, the i.p. administration of 5.0 mg/kg indomethacin 15–20 min prior to the micro-injection entirely blocked this rise in T_b induced in the rat by IL-11. The mean increase in T_b produced by IL-11 was statistically higher than that following both the pretreatment with indomethacin ($F_{[1,98]} = 78.12$, $P < 0.05$) and the micro-injection of CSF ($F_{[1,98]} = 116.91$, $P < 0.05$).

DISCUSSION

The present results demonstrate that IL-11 induces a fever when the cytokine is delivered directly onto the neurons of the thermosensitive AH/POA. The finding that the febrile response is dose dependent suggests that the action of IL-11 represents a specific

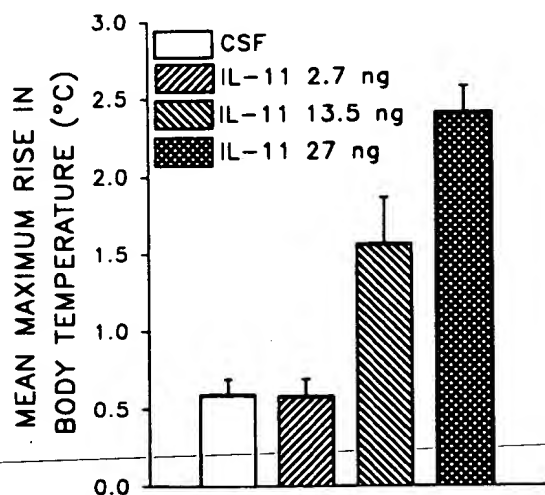


Fig. 3. Histogram depicting mean \pm SE maximum increase in T_b ($^{\circ}\text{C}$) of individual rats during the 8.0 hr interval after micro-injection into AH/POA of CSF control ($N = 15$), 2.7 ng IL-11 ($N = 6$); 13.5 ng IL-11 ($N = 8$); and 27 ng IL-11 ($N = 8$). N = number of experiments.

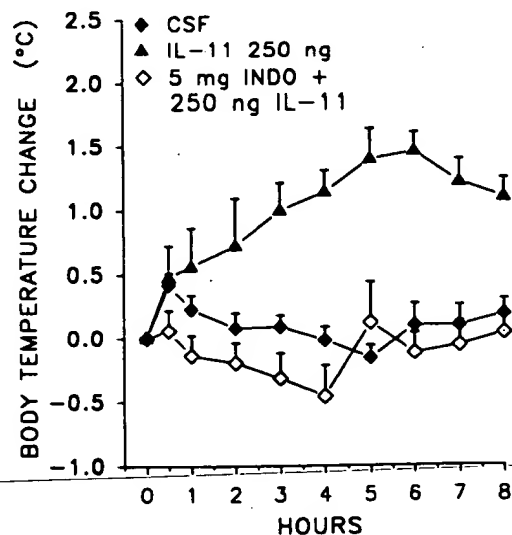


Fig. 4. Mean \pm SE change from baseline T_b ($^{\circ}\text{C}$) at time zero of rats after micro-injection into AH/POA of CSF control ($N = 15$), 250 ng IL-11 ($N = 5$), and 5.0 mg/kg of indomethacin ($N = 5$) given i.p. 15–20 min before the micro-injection of 250 ng of IL-11.

neuropharmacological reaction to the presence of the cytokine within the neuronal parenchyma. The characteristics of the rise in T_b of the rat are very similar in terms of dose, magnitude of elevation and time course to those observed with other cytokines comprising the family of interleukins (Blatteis *et al.*, 1990; Myers *et al.*, 1994). Anatomically, the locus of action of IL-11 within the ventral diencephalon is concordant with the classical circumscribed area which contains neurons sensitive to a displacement of body temperature as well as to a pyrogen challenge (Myers, 1980).

The pharmacological blockade by indomethacin of the febrile response to IL-11 provides incipient evidence that a prostaglandin of the E series synthesized *de novo* within cells of the diencephalon may serve, in part, as a mediator of the IL-11-induced fever. In fact, this observation corresponds closely to the inhibition of a fever by prostaglandin synthesis inhibitors, of other known pyrogenic cytokines such as IL-1 and IL-6 (Blatteis *et al.*, 1990; Hashimoto, 1991; Myers *et al.*, 1994). Thus, IL-11 most likely functions to evoke thermogenesis by way of the cyclo-oxygenase cascade rather than through an alternative pathway which is independent of a PGE and involves another of the cytokines, MIP-1 (Miñano *et al.*, 1991; Simpson *et al.*, 1994). The difference in the efficacy of the batch of IL-11 used in the indomethacin experiments, compared to that used for the dose response analysis, was due apparently to its lower specific activity as determined by the T10 proliferation assay. Since the specific activity of the cytokine was approximately one-half that of the other, then about twice the dose was required to evoke a similar T_b response. Another variable in the difference between the batches of IL-11 could be the rate of degradation of the two cytokines at a temperature in the cerebral tissue of 37°C.

The reduction in the intake of food following the micro-injection of the 27 ng dose of IL-11 into AH/POA coincides with the anorexigenic effects observed following the central administration of other pyrogenic cytokines including MIP-1, tumor necrosis factor and IL-1 (Masotto *et al.*, 1992; Miñano and Myers, 1991; Myers *et al.*, 1993; Plata-Salaman *et al.*, 1988). However, since the inhibitory action of IL-11 on feeding occurs concurrently with the fever, it is conceivable that the effect on food intake is a secondary consequence of the febrile component of the acute phase response rather than a specific action on the central mechanisms in the hypothalamus which govern caloric intake. In this connection, the fever and the anorexia produced by the most potent hyperthermic cytokine, MIP-1, is entirely dissociated anatomically. That is, when infused into the ventromedial hypothalamic area of the rat, MIP-1 produces only anorexia without affecting the T_b of the animal (Miñano and Myers, 1991). However, after the injection of MIP-1 into the AH/POA, the condition of anorexia is associated with an ensuing fever.

Since its initial discovery, IL-11 has shown characteristics common to other cytokines (Burstein *et al.*, 1992;

Baumann and Schendel, 1991; Hu *et al.*, 1993). IL-11 shares signal transduction pathways with other cytokines, particularly IL-6 (Hu *et al.*, 1993; Yin *et al.*, 1992) in spite of its specific action on cell membrane receptors. However, the present experiments demonstrate that IL-11 *in vivo* exerts a clear-cut action on neurons in the brain. The action of the cytokine on the AH/POA may ensue as result of its access to the organum vasculosum lamina terminalis (OVLT) from the periphery (Blatteis, 1992), or by its penetration directly through the blood brain barrier (Johansson, 1992), or perhaps by means of its synthesis within the parenchyma of the brain itself. Recently it was shown that IL-11 stimulates neural differentiation *in vitro* which is concordant also with the *in vitro* effect of IL-6 (Mehler *et al.*, 1993). The latter findings thus infer that IL-11 also may have the capacity to act on cells of the brain in the initial stages of cerebral development.

Finally, although our results indicate a role of IL-11 in the progression of events leading to a fever, its functional significance in comparison to that of MIP-1 and the members of the interleukin family is not yet clear. If the cellular findings on the hematopoietic mechanism and immune systems can be extrapolated to the brain, the endogenous activity of IL-11 may be one of synergism with other cytokines in the complex communication between the immune system and the central nervous system.

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